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EXAMINER

MAIER, LEIGH C

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 28

Application Number: 09/527,558
Filing Date: March 16, 2000
Appellant(s): PFIRRMANN, ROLF W.

George R. Repper
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 25, 2003.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is essentially correct. However, the examiner notes that at page 3, second full paragraph, Appellant alludes to purported unexpected results. This is mentioned in the specification, but no supporting evidence has been provided by Appellant.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

Appellant's brief includes a statement that claims 1-4, 13, and 24-34 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

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(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

WO 98/28027	LEHNER	7-1998
5,077,281	REINMULLER	12-1991
5,688,516	RAAD et al	11-1997
5,167,960	ITO et al	12-1992

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 U.S.C. § 103

Claims 1-4 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over LEHNER (WO 98/28027) in view of REINMULLER (US 5,077,281).

The claims are drawn to a method of preventing thrombosis formation on a liquid-containing surface of a liquid-delivery system comprising a regimen of forming a seal in the system containing taurolidine, taurultam, or a mixture thereof and an anticoagulant agent, other than taurolidine or taurultam.

LEHNER discloses flushing a port delivery system with 2 ml of a solution comprising a thrombosis-preventing amount, 800 IU, of the anticoagulant, heparin. At about 150 IU/mg, the solution would contain about 5.3 mg of heparin. This flushing is followed by sealing the system with 2% by weight of taurolidine for 12 hours. See page 9, lines 8-23. The exemplified weight

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percent of taurolidine falls well in the claimed range. The reference further teaches the replacement of the sealing liquid as needed after use for therapeutic treatment of administration or parenteral nutrition. In the latter case, particularly, this would require replacement of sealing liquid at least about daily.

The process is not explicitly termed "a method for preventing thrombosis formation." However, the reference teaches that taurolidine has the further advantage that it can reduce the adhesiveness of fibrin deposits. See sentence bridging pages 8 and 9. One of ordinary skill would recognize that fibrin deposition leads to thrombosis formation.

LEHNER further does not teach the addition of another anticoagulant agent other than taurolidine, taurultam, or a mixture thereof in the "sealing liquid."

REINMULLER teaches a small genus of taurolin derivatives having bactericidal and coagulation-inhibiting action. This genus includes taurolidine (also known as taurolin) and taurultam, species which are the preferred compounds in the genus. The reference specifically suggests their use in extracorporeal circulation. See col 1, lines 40-47 and col 3, lines 27-62. REINMULLER teaches that contact of a solution of taurolin (taurolidine) renders a surface thromboresistant. REINMULLER further teaches the utility of using taurolidine or taurultam together with another anticoagulant agent, such as heparin. See col 4, lines 33-40.

Given that REINMULLER had taught that taurolidine has the inherent property of rendering a surface thromboresistant, sealing taurolidine in a liquid delivery system is in fact a method for preventing thrombosis formation. It would have been obvious to one having ordinary skill in the art at the time the invention was made to seal taurolidine and another coagulant in a liquid delivery system for the purpose of preventing thrombosis formation with a reasonable

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expectation of success. One of ordinary skill would be motivated to add an anticoagulant for the additive effect. It would be within the scope of the artisan to determine the optimum amount of additional anticoagulant through routine experimentation.

Claims 24-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over LEHNER (WO 98/28027) in view of RAAD et al (US 5,688,516).

The claims are drawn to a method of preventing thrombosis formation on a liquid-containing surface of a liquid-delivery system comprising a regimen of: (1) first contacting surface with solution containing an anticoagulant agent other than taurolidine or taurultam; (2) thereafter contacting said surface with a solution containing taurolidine, taurultam, or a mixture thereof; and (3) repeating the contacting steps between delivery of liquids.

LEHNER teaches as set forth above. The reference teaches repeating the step of contacting or flushing with taurolidine or tarultam, but not another anticoagulant agent. See page 10, lines 4-12. LEHNER, therefore, teaches two-and-a-half of the three steps of the instant method.

Thrombotic occlusion in the lumen of a catheter is a known complication. RAAD teaches that prophylactic flushing of a catheter with heparin to prevent this complication is the standard of care. See col 1, lines 27-43. RAAD also teaches that other known anticoagulants, such as citrate and hirudin, have utility in antithrombotic prophylaxis and that this type of treatment is beneficial to a variety of medical liquid delivery systems. See col 5, lines 24-35 and col 6, lines 14-27.

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It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the process of treating a liquid delivery system as taught by LEHNER by repeating both contacting steps for the additional antithrombotic prophylaxis, as taught by RAAD. The artisan would be motivated to repeat these steps after liquid delivery in order to clear away any remaining delivered material, maintain patency, and prevent infection. One of ordinary skill would reasonably expect thrombosis prevention upon treating the delivery system with two anticoagulants, known to be beneficial for this purpose. It would be within the scope of the artisan to select any appropriate anticoagulant for this purpose for use in combination with the taurolin derivative.

Claims 24-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over LEHNER (WO 98/28027) and RAAD et al (US 5,688,516) and further in view of ITO et al (US 5,167,960).

The invention is as set forth above. Claim 33 recites a number of anticoagulant species.

LEHNER and RAAD teach as set forth in the previous Office action. These references do not teach the full range of anticoagulants recited in claim 33. However, as set forth above, RAAD does expressly suggest the use of other anticoagulants.

ITO teaches the use of other thrombogenesis inhibitors, such as hirudin and ticlopidine, in liquid delivery systems. See abstract and col 1, lines 44-50.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the LEHNER process by first flushing the liquid-delivery system with an anticoagulant, as is the standard of care taught by RAAD, as discussed above. It

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would have been within the scope of the artisan to select any known thrombogenesis inhibitor for this purpose. It would be in the scope of the artisan to optimize the amount of thrombogenesis inhibitor with routine experimentation.

(11) Response to Argument

1. Appellant argues that claims 1-4 and 13 are nonobvious over Lehner and Reinmuller

Appellant first argues that each reference does not teach every limitation of the invention. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references, which is the case in the outstanding rejection.

Appellant further contends that there is no motivation in the prior art for the proposed combination because Lehner is concerned with the prevention of infection or sepsis while Reinmuller is directed to the prevention of thrombosis. As Appellant quotes the examiner in paper no. 22:

Lehner teaches that taurolidine can reduce the adhesiveness of fibrin deposits that lead to thrombosis. Furthermore, Reinmuller also recognizes the dual functionality (bacteriocidal and coagulation-inhibiting action) of the taurolin derivatives in the reference. The examiner maintains that one of ordinary skill, having the teaching of Lehner and Reinmuller, would recognize that sealing a taurolin derivative alone would reasonably expected to prevent thrombosis. The addition of another anticoagulant would be obvious for the additive effect.

The examiner maintains that this is valid and sufficient motivation for combining the references of record to derive the instant method.

Appellants then make the following allegation:

First of all, there are no inherent anti-coagulant activities of taurolidine or taurultam. Reinmuller was mistakenly lead [sic] to this belief because the blood he used was blood for transfusion and already contained heparin.

Appellant presents this allegation as a statement of fact with no supporting evidence. Further, this is the first time in prosecution history that Appellant has raised this issue. Moreover, it is also noted that claim 1 recites "said thrombosis-preventing liquid further containing an anticoagulant agent *other than* taurolidine or taurultam." (Emphasis added.) This claim wording appears to tacitly concede that taurolidine and taurultam are anticoagulant agents.

Based on the aforementioned unsupported allegation, Appellant appears to conclude that any anticoagulant activity of the taurolin derivatives is simply based on the examiner's opinion. However, as can be clearly seen, Reinmuller teaches that taurolin derivatives have coagulation-inhibiting activity. At the time the invention was made, one of ordinary skill would have no reason to doubt the validity of the teaching of Reinmuller and would reasonably expect success in combining this teaching with Lehner.

Finally, Appellant concludes that the examiner's conclusion of obviousness is based upon improper hindsight reasoning. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellant's disclosure, such a reconstruction is proper. This has been clearly established in the discussion above.

Appellant argues that claims 2-4 each stand alone. For each claim, Appellant argues that the combination of Lehner and Reinmuller do not teach the method with these particular time limitations. However, as discussed above, Lehner teaches sealing the system with 2% of taurolidine for 12 hours, which would include "at least about 1 hour." The reference further

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teaches the replacement of the sealing liquid as needed after use for therapeutic treatment or administration of parenteral nutrition. In the latter case, particularly, this would require replacement of sealing liquid at least about daily.

2. Appellant argues that claims 24-34 are nonobvious over Lehner in view of Raad

Appellant contends that neither reference suggests repeating the two steps, as recited in claim 24. This was clearly stated in the rejection. However, the motivation for this repetition is discussed above.

Appellant further sets forth the newly raised argument that Raad actually teaches away from the repetitive two-step process because the reference is “directed towards an isolated instance of flushing or coating a catheter with an solution of anticoagulants and antibiotics.” Applicant appears to be arguing that Raad teaches contacting the catheter once and never again. The examiner disagrees with this characterization of the reference. The reference clearly contemplates flushing the medical device as necessary. See, for example, col 9, lines 5-14.

Appellant concludes arguments regarding the independent claim by contending that the basis for combining the references is unsupported. Again, as discussed above, Lehner exemplifies contacting the device with heparin (an anticoagulant) followed by contacting with taurolidine and teaches repeating the taurolidine step between liquid deliveries. The examiner maintains that it would be obvious to repeat both steps for the additive effects.

Appellant states that claim 28 stands alone and contends that the references do not teach the limitation of injecting then removing the anticoagulant. As addressed above, Lehner teaches flushing the port delivery system with heparin, followed by sealing with taurolidine, not a

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combination of heparin and taurolidine. If it is Appellant's position that this flushing does not include removal of the heparin, Appellant cannot then argue that Lehner does not teach or suggest the use of a composition comprising both (1) taurolidine or taurultam and (2) an anticoagulant agent other than taurolidine or taurultam. (See argument above regarding claims 1-4 and 13.)

Appellant argues that the sets of claims, 25 and 29, 26 and 30, 27 and 31, each stand alone. For each set, Appellant argues that the combination of Lehner and Raad do not teach the method with these particular time limitations. However, as discussed above, Lehner teaches sealing the system with 2% of taurolidine for 12 hours, which would include "at least about 1 hour." The reference further teaches the replacement of the sealing liquid as needed after use for therapeutic treatment or administration of parenteral nutrition. In the latter case, particularly, this would require replacement of sealing liquid at least about daily.

Appellant argues that claim 33 and 34 stand alone. Appellant argues that the combination of Lehner and Raad do not teach the method with these particular anticoagulants in the recited amount. However, both Lehner and Raad teach the use of heparin, as recited in claim 33, with Lehner teaching an amount recited in claim 34. Furthermore, Raad teaches the use of other anticoagulants, such as citrates.

3. Appellant argues that claims 24-34 are nonobvious over Lehner and Raad in view of Ito

Appellant contends that "[t]he Examiner is of the opinion that Ito teaches anticoagulants including hirudin and its derivatives. . ." The examiner does not find it to be a matter of opinion, but fact, that Ito does teach that a number of recited compounds, such as hirudin and ticlopidine,

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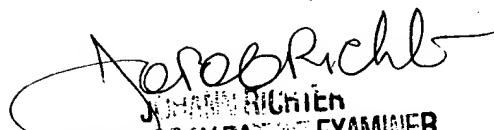
are known anticoagulants. The combination of Lehner and Raad teach as set forth above. It would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings to derive the instant method. It would be further obvious to select any known anticoagulant, as suggested by Raad, to use in said method.

With regard to the dependent claims, this section sets forth no arguments that have not already been addressed above.

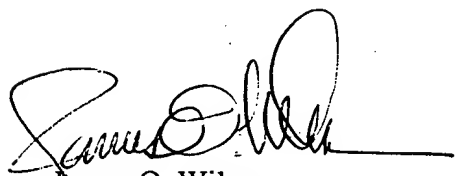
Appellant has recited two methods for preventing thrombosis formation using tauroliding or taurultam and an anticoagulant, in combination or sequentially. The methods have been made obvious by the art of record. For the above reasons, it is believed that the rejections should be sustained.


Respectfully submitted,

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December 9, 2003


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